DATA EVALUATION RECORD

NOA 446510 (MANDIPROPAMIDE)

Study Type: OPPTS 870.4200b [§83-2b]; Carcinogenicity Study in Mice

Work Assignment No. 4-1-121 I; formerly 3-1-121 I (MRID 46800233)

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DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity study in mice [dietary]; OPPTS 870.4200b [§83-2b]; OECD 451.

PC CODE: 036602 **DP BARCODE**: D328539
TXR#: 0054273

TEST MATERIAL (PURITY): NOA 446510 (Mandipropamide; 96.5% a.i.)

SYNONYMS: 4-chloro-*N*-[2-[3-methoxy-4-(2-propynyloxy)phenyl]ethyl]-α-(2-propynyloxy)benzeneacetamide

CITATION: Milburn, G. (2005) NOA446510: 80 week carcinogenicity study in mice. Central Toxicology Laboratory, Macclesfield, Cheshire, UK. Laboratory Study No: CTL/PM1275/Regulatory/Report; Syngenta No.: T004628-02, November 11, 2005. MRID 46800233. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, P.O. Box 18300, Greensboro, NC

EXECUTIVE SUMMARY – In a carcinogenicity study (MRID 46800233), NOA 446510 (Mandipropamide; 96.5% a.i.; Batch No. SEZ2BP007) was administered in the diet to C57BL/10J$_f$CD-1 mice (50/sex/dose) at dose levels of 0, 100, 500, or 2000 ppm (equivalent to 0/0, 10.6/13.2, 55.2/67.8, and 222.7/284.6 mg/kg bw/day in males/females) for up to 80 weeks.

No adverse treatment-related effects were observed on mortality, food consumption, hematology (i.e., leukocyte differential), gross pathology, or histopathology.

An increased frequency of circling behavior was observed in the females at 500 and 2000 ppm. However, this behavior was only slightly increased in incidence at 2000 ppm compared to controls. Dose-related increases in the number of mice with their left ear being torn were observed in both sexes at 500 and 2000 ppm. The number of mice with the right ear torn was minimal in incidence (<=1 mouse/dose group) and did not show a pattern with dose. It was stated that the animals were identified by ear tags, and it is likely that these identification tags were placed in the left ear. The mice were housed together in groups and could have removed the tags (and selectively torn the left ear) of their cage-mates via fighting or other interactions.

However, this would not explain why the incidence of this finding was dose-related. The possibility that the test substance increased fighting or some other behavior that led to the left ear being torn cannot be ruled out. However, because there were no dose-related incidences in scabs or other signs of fighting and because there were no clinical signs of neurotoxicity in this study or in the acute or subchronic neurotoxicity studies in rats (MRID 46800240 through 46800242), the toxicological importance of this finding is considered equivocal.

At 2000 ppm, body weights were slightly decreased ($p \leq 0.05$) in the males generally from Weeks 19-35 and in the females during Weeks 4, 5, and 13-81. Cumulative weekly body weight gains were decreased at this dose in the males during Weeks 19-81 and in the females during Weeks 4-6 and 11-81. The decreased body weight gains attained statistical significance ($p \leq 0.05$) throughout the study, except at Week 81 in the males and at Week 79 in the females. Food utilization was decreased ($p \leq 0.05$) in the males for Weeks 9-13 (decr. 20%) and Weeks 1-13 (decr. 5%) and in the females for Weeks 1-4 (decr. 12%) and reflected the decrease in body weights at this dose. The decreases in body weights were not considered to be of biological or toxicological significance.

Absolute, relative to body weight, and adjusted for initial body weight liver weights were increased in the males at 500 ppm and in both sexes at 2000 ppm. These increases were significant ($p <= 0.05$) except for absolute weights in the 2000 ppm males (relative liver weights were not examined statistically). In the absence of any microscopic findings in the liver, the relatively small increases in liver weights were not considered adverse but were likely an adaptive response to the presence of the test substance.

At the doses tested, there were no effects of treatment on the incidence or time to onset of any tumor types. Therefore, there was no evidence of a carcinogenic effect. Dosing was considered adequate based on decreased body weight and body weight gain.

The LOAEL is 2000 ppm (equivalent to 223/285 mg/kg/day in males/females), based on decreased body weight gain in both sexes and decreased food utilization in males. The NOAEL is 500 ppm (equivalent to 55/68 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

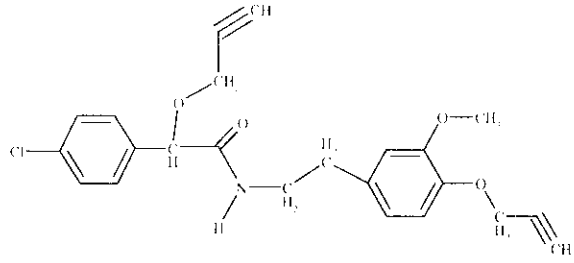
COMPLIANCE - Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: NOA 446510 (Mandipropamide)

Description: Slightly beige solid
Batch No.: SEZ2BP007
Purity: 96.5% a.i.
Compound stability: Stable in the diet for up to 44 days at room temperature
CAS # of TGAI: 374726-62-2
Structure:



2. Vehicle and/or positive control: Diet

3. Test animals

Species: Mouse
Strain: C57BL/10J;CD-1
Age/weight at study initiation: Approximately 34-38 days old; 17.9-25.9 g males; 15.4-21.2 g females
Source: AstraZeneca Biological Services Section, Alderley Park, Macclesfield, Cheshire, UK)
Housing: Housed in groups of up to 5 mice by common sex and dose in multiple racks
Diet: CT1 diet (Special Diets Services Ltd., Stepfield, Witham, Essex, UK), *ad libitum*
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: 22 ± 3°C
Humidity: 30-70%
Air changes: ≥15 air changes/hour
Photoperiod: 12 hours light/12 hours dark
Acclimation period: Approximately 5 days

B. STUDY DESIGN

1. In life dates: Start: April 21, 2003 End: Approximately October 24, 2004

2. Animal assignment: Animals were randomly assigned, stratified by body weight, to the test groups presented in Table 1.

TABLE 1: Study design [a]

Test group	Dose to animal (ppm)	Dose to animal (mg/kg/day in M/F)	No. mice/sex
Control	0	0/0	50
Low	100	10.6/13.2	50
Mid	500	55.2/67.8	50
High	2000	222.7/284.6	50

a Data were obtained from pages 18, 34, and 35 of MRID 46800233.

3. **Dose-selection rationale:** Doses were selected on the basis of results from two previously conducted dietary toxicity studies in mice (submitted concurrently). In a 28 day study (MRID 46800217), dietary inclusion levels of 0, 700, 2100, and 7000 ppm were tested. At 2100 and 7000 ppm, the following findings were noted: (i) initial weight loss and decreased food consumption in females; (ii) decreased bodyweights in both sexes; (iii) decreases in a number of red cell parameters in females; (iv) increased liver weights in both sexes; and (v) decreased spleen weights in females. Additionally at 7000 ppm: initial weight loss, decreases in a number of red cell parameters, and decreased spleen weights were observed in the males; and an increased incidence of hepatic periportal eosinophilia and hypertrophy was noted in both sexes. In a subsequent 90 day study (MRID 46800213), mice were fed diets at 0, 300, 800, 2000, or 5000 ppm. Liver weights were increased at ≥800 ppm. At 2000 and 5000 ppm, the following effects of treatment were noted: (i) decreased body weight and body weight gains in both sexes; (ii) decreased food consumption in males; (iii) decreases in a number of red cell indices in females; (iv) decreased spleen weights in females; and (v) hepatic periportal eosinophilia in the majority of females. Additionally at 5000 ppm: food consumption was decreased in females; red cell indices were decreased in the males; and hepatic periportal eosinophilia was noted in half of the males.

4. **Treatment preparation, administration, and analysis:** Dietary formulations were prepared in 1 kg premixes by triturating the appropriate amount of test substance with milled diet. The test diets were prepared for each dose level by mixing each premix with additional diet to achieve the targeted concentration. Dietary formulations were stored at room temperature until use and were fed for a maximum of 44 days. The stability of the test substance in 100 and 10,000 ppm dietary formulations was tested for up to 44 days at room temperature in a separate study (Report No. CTL/WK0441/ Regulatory/Report; data presented in MRID 46800216, concurrently submitted). The homogeneity (top, middle, bottom) of the test substance in the diet was tested at 100 and 2000 ppm prior to treatment. Concentrations at each dietary level were measured prior to the start of the study and at intervals of approximately two to three months throughout the study.

Results

Homogeneity: -4.6-2.8% C.V.

Stability: 101.4-103.5% nominal

Concentration: 96.1-107.2% nominal

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

5 **Statistics:** The following statistical tests were applied to the data:

PARAMETER	ANALYSIS CONDUCTED
Body weight	Analysis of covariance (ANCOVA) on initial (Day 1) body weight
Food consumption Food utilization Hematology	Analysis of variance (ANOVA)
Organ weights	ANOVA and ANCOVA on final body weight
Mortality	Kaplan-Meier survival estimates were calculated. Pair-wise comparison of each treated group with controls and an overall trend test were performed using a logrank test (Peto and Pike, 1973).
Tumor incidence	Pair-wise comparison of each treated group with controls using Fisher's Exact Test. Test for trend using Cochran-Armitage Test. Analyses were conducted on the incidence of tumors from intercurrent deaths, terminal kill, and total combined, and for animals surviving to time of first incidence.
Time to tumor	Prevalence analysis (assuming tumors were incidental), death rate analysis (assuming all tumors were observed in a fatal context), and a combined analysis (allowing for the observed context as described in Peto et. al.).

All data were evaluated using the MIXED procedure in SAS. Least-squares means were calculated for each group, and each treated group was compared to the control using a 2-sided Student's t-test, based on the error mean square in the analysis. Significance was denoted at 5 and 1% probability.

The assumptions of normal distribution of the data and homogeneity of variances should have been verified prior to proceeding with parametric analyses. Otherwise, the statistical analyses were considered appropriate.

C. METHODS

1. Observations

a. **Cageside observations:** Animals were observed twice daily for mortality and clinical signs of toxicity.

b. **Clinical examinations:** Detailed clinical observations were performed prior to treatment and weekly throughout the study.

2. **Body weight:** All animals were weighed prior to treatment, weekly from Weeks 1 through 15 and every 2 weeks thereafter throughout the remainder of the study, and at necropsy. Cumulative body weight gain was reported at each of these intervals.

3. **Food consumption and compound intake:** Food consumption was recorded continuously for each cage of mice through Week 16, and thereafter every fourth week throughout the remainder of the study. Mean food consumption (g food/animal/day) was reported at these weekly intervals for each cage (n=10). Food utilization (5 mice/cage x 2 cages = 10 mice/sex/group) was calculated as the bodyweight gained by the mice in the cage per 100 g of food eaten for Weeks 1-4, 5-8, 9-13, and 1-13. Test substance intake (mg/kg body

weight/day) was calculated for each of the intervals for which body weight and food consumption data were reported and for the overall (Weeks 1-80) study using the nominal dietary concentration and the food consumption and body weight data.

4. **Ophthalmoscopic examination**: The eyes were not examined.

5. **Hematology and clinical chemistry**: During Week 53, all mice were bled from the tail vein, and blood smears were prepared but were not evaluated. At scheduled termination, all surviving animals were bled by cardiac puncture, and a white blood cell differential was performed. No other hematology or clinical chemistry analyses were conducted.

	Hematocrit (HCT)	X	Leukocyte differential count*
	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
	Leukocyte count (WBC)		Mean corpuscular HGB concentration (MCHC)
	Erythrocyte count (RBC)		Mean corpuscular volume (MCV)
	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Activated partial thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Minimum required to carcinogenicity studies (control and high dose unless effects are observed) based on Guideline 870.4200 and OECD 451.

6. **Urinalysis**: Urinalysis was not performed, but is not required based on Guideline 870.4200.

7. **Sacrifice and pathology**: Except for animals found dead, all mice (including any killed prematurely) were euthanized by overdose of halothane Ph. Eur. anesthesia followed by exsanguination. All animals were subjected to a gross necropsy, and the following CHECKED (X) tissues were collected. Additionally, the (XX) organs from all mice sacrificed on schedule were weighed (paired organs weighed together).

	DIGESTIVE SYSTEM
	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver*+ [a]
XX	Gall bladder (not rat)*+ [a]
	Bile duct (rat)
X	Pancreas*
	RESPIRATORY
X	Trachea*
X	Lung*++
X	Nose*
X	Pharynx*
X	Larynx*

	CARDIOVASC./HEMAT.
X	Aorta, thoracic*
XX	Heart*+
X	Bone marrow*
X	Lymph nodes*
XX	Spleen*+
X	Thymus
	UROGENITAL
XX	Kidneys*+
X	Urinary bladder*
XX	Testes*+
XX	Epididymides*+
X	Prostate*
X	Seminal vesicles*
XX	Ovaries*+
XX	Uterus*+ (including cervix)
X	Mammary gland* (female only)
X	Vagina
X	Oviduct
X	Preputial gland

	NEUROLOGIC
XX	Brain (multiple sections)*+
X	Peripheral nerve*
X	Spinal cord (3 levels)*
X	Pituitary*
X	Eyes (retina, optic nerve)*
	GLANDULAR
XX	Adrenal gland*+
	Lacrimal gland
X	Parathyroids*
X	Thyroids*
	OTHER
X	Bone (sternum and/or femur)
X	Skeletal muscle
X	Skin*
X	Stifle Joint
X	All gross lesions and masses*
X	Harderian gland

* Required for carcinogenicity studies based on Guideline 870.4200
\+ Organ weights required in carcinogenicity studies.
++ Organ weight required if inhalation route.
a The liver and gall bladder were weighed together.

It was stated that each tissue was fixed in an appropriate fixative. All tissues were processed routinely, stained with hematoxylin and eosin, and examined using light microscopy.

I. RESULTS

A. OBSERVATIONS

1. **Mortality**: No treatment-related effect was observed. Mortality ranged from 84 to 94% at 18 months (Table 2). Thus, the guideline requirements of 50% survival at Week 65 and 25% survival at Week 78 were met.

TABLE 2. Mortality and disposition [# animals (study weeks)] in mice fed NOA 446510 in the diet for up to 80 weeks [a]				
Disposition	Dose (ppm)			
	0	100	500	2000
Males				
Found dead	0	2 (Weeks 66,80)	3 (Weeks 56-74)	5 (Weeks 46-78)
Killed for humane reasons	1 (Week 67)	0	0	0
Killed due to clinical signs	4 (Weeks 56-81)	1 (Week 68)	5 (Weeks 46-75)	1 (Week 8)
Killed termination	45	47	42	44
Survival (%) [b]	45/50 (90%)	47/50 (94%)	42/50 (84%)	44/50 (88%)
Females				
Found dead	4 (Weeks 45, 68, 74, 79)	0	2 (Weeks 23, 24)	4 (Weeks 8-73, 80)
Killed for humane reasons	0	0	0	1 (Week 69)
Killed due to clinical signs	2 (Weeks 60, 79)	5 (Weeks 49-80)	3 (Week 8-75)	2 (Week 47, 61)
Killed termination	44	45	45	43
Survival (%) [b]	44/50 (88%)	45/50 (90%)	45/50 (90%)	43/50 (86%)

a Data were obtained from Table 6 on pages 39, 40, and 42-44 of MRID 46800233.
b Calculated by the reviewers from data presented in this table.

2. **Clinical signs:** Selected clinical observations are included in Table 3. An increased frequency of circling behavior was observed in the females at 500 ppm (34 observations) and 2000 ppm (110 observations). However, the incidence of this behavior at 500 ppm (2 mice) was comparable to controls (2 mice) and was only slightly increased at 2000 ppm (4 mice). Dose-related increases in the number of mice with their left ear being torn were observed in both sexes at 500 ppm (7-9 mice) and at 2000 ppm (16-17 mice). The number of mice with the right ear torn was minimal in incidence (≤1 mouse/dose group) and did not show a pattern with dose. No other clinical signs could be attributed to treatment.

TABLE 3. Selected clinical signs [# animals (# observations)] in mice fed NOA 446510 in the diet for up to 80 weeks [a]				
Observation	Dose (ppm)			
	0	100	500	2000
Males				
Left ear torn	1 (12) Weeks 3-14	1 (10) Weeks 15-24	9 (546) Weeks 1-82	17 (1045) Weeks 1-82
Right ear torn	0	0	1 (49) Weeks 35-81	1 (82) Weeks 1-82
Females				
Circling	2 (4) Weeks 37-40	1 (4) Weeks 79-81	2 (34) Weeks 65-81	4 (110) Weeks 35-82
Left ear torn	5 (356) Weeks 2-81	5 (296) Weeks 3-81	7 (512) Weeks 1-82	16 (1063) Weeks 2-82
Right ear torn	1 (66) Weeks 17-81	0	0	1 (9) Weeks 63-69

a Data were obtained from Table 6 on pages 40, 42, and 44 of MRID 46800233.

B. <u>BODY WEIGHT AND BODY WEIGHT GAIN</u>: At 2000 ppm, body weights (Table 4a) were decreased ($p \leq 0.05$) in the males generally from Weeks 19-35 (↓3-4%) and in the females during Weeks 4, 5, and 13-81 (↓2-7%). For both males and females, there was just the suggestion of lower body weights throughout the study (not more than a 7% decrease from controls; < one S.D. difference). Weekly cumulative body weight gains (Table 4b) were decreased at this dose in the males during Weeks 19-81 (↓7-13%; $p \leq 0.05$, except not significant [NS] at Week 81) and in the females during Weeks 4-6 and 11-81 (↓7-15%, except NS at Week 79). There was a 9% decrease in body weight gains compared with controls (both sexes) when body weight gains were calculated by 13-week intervals).

At 500 ppm, incidental differences ($p \leq 0.05$) from controls were noted in: body weights in the males during Weeks 2 and 49 (↑2-3%) and in the females during Week 31 (↓3%); and in body weight gains in the males during Week 2 (↑29%) and in the females during Week 31 (↓8%).

At 100 ppm, body weights and body weight gains were comparable to controls throughout the study.

TABLE 4a. Mean (±SD) absolute and mean adjusted (for initial weight) body weights at selected intervals in mice fed NOA 446510 in the diet for up to 80 weeks [a]

Study Week	Dose (ppm)			
	0	100	500	2000
Males				
1	21.9 ± 1.4	21.7 ± 1.2	21.7 ± 1.3	21.4 ± 1.7
14 (unadjusted)	32.3 ± 2.1	32.2 ± 2.0	32.1 ± 1.9	31.3 ± 2.4
14 (adjusted)	32.0	32.1	32.0	31.6
19 (unadjusted)	34.5 ± 2.5	34.1 ± 2.3	34.4 ± 2.3	32.9 ± 2.6
19 (adjusted)	34.3	34.0	34.3	33.3* (↓3)
35 (unadjusted)	40.1 ± 4.5	39.8 ± 3.7	40.4 ± 4.3	37.5 ± 4.1
35 (adjusted)	39.7	39.7	40.3	38.2* (↓4)
53 (unadjusted)	43.6 ± 5.2	42.9 ± 4.3	44.5 ± 4.6	40.9 ± 5.1
53 (adjusted)	43.2	42.8	44.2	41.7
81 (unadjusted)	44.4 ± 6.3	43.9 ± 4.9	44.4 ± 6.7	41.9 ± 5.2
81 (adjusted)	43.8	44.0	44.1	42.7
Females				
1	17.7 ± 1.0	18.0 ± 1.1	17.9 ± 1.1	18.0 ± 0.9
4 (unadjusted)	20.9 ± 1.1	21.0 ± 0.9	21.0 ± 1.0	20.7 ± 1.0
4 (adjusted)	21.0	21.0	21.0	20.6* (↓2)
5 (unadjusted)	22.0 ± 1.2	22.1 ± 1.3	21.9 ± 1.2	21.8 ± 1.2
5 (adjusted)	22.1	22.1	21.9	21.7* (↓2)
13 (unadjusted)	25.1 ± 1.3	25.2 ± 1.6	25.4 ± 1.7	24.8 ± 1.2
13 (adjusted)	25.2	25.2	25.4	24.7* (↓2)
14 (unadjusted)	25.2 ± 1.2	25.5 ± 1.5	25.3 ± 1.6	24.9 ± 1.2
14 (adjusted)	25.4	25.5	25.3	24.9* (↓2)
53 (unadjusted)	32.0 ± 3.6	32.0 ± 3.6	32.0 ± 3.3	30.7 ± 2.8
53 (adjusted)	32.3	31.9	32.0	30.5** (↓6)
65 (unadjusted)	33.4 ± 3.7	32.9 ± 3.7	33.1 ± 3.2	31.8 ± 3.0
65 (adjusted)	33.8	32.9	33.1	31.6** (↓7)
81 (unadjusted)	34.0 ± 4.1	34.4 ± 4.1	34.8 ± 3.5	32.8 ± 3.5
81 (adjusted)	34.3	34.3	34.8	32.5* (↓5)

a Data (n = 42-50) were obtained from Table 7 on pages 47-62 of MRID 46800233. Percent differences from controls, calculated by the reviewers, are included in parentheses.

* Significantly different from controls at p#0.05

** Significantly different from controls at p#0.01

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TABLE 4b. Cumulative mean (±SD) body weight gains at selected intervals in mice fed NOA 446510 in the diet for up to 80 weeks [a]

Study Interval	Dose (ppm)			
	0	100	500	2000
Males				
Weeks 1-14	10.4 ± 1.5	10.4 ± 1.5	10.4 ± 1.4	9.9 ± 1.7
Weeks 1-19	12.6 ± 2.0	12.3 ± 2.0	12.6 ± 1.9	11.5 ± 2.1** (↓9)
Weeks 1-23	13.5 ± 2.4	13.5 ± 2.1	13.5 ± 2.2	12.5 ± 2.5* (↓7)
Weeks 1-53	21.7 ± 4.4	21.1 ± 3.7	22.7 ± 4.2	19.5 ± 4.5** (↓10)
Weeks 1-71	23.1 ± 5.3	22.6 ± 4.0	24.0 ± 5.0	20.1 ± 4.2** (↓13)
Weeks 1-81	22.4 ± 5.8	22.2 ± 4.4	22.6 ± 6.5	20.5 ± 4.7 (↓8)
Females				
Weeks 1-4	3.1 ± 0.8	3.1 ± 0.8	3.1 ± 0.8	2.7 ± 0.9** (↓13)
Weeks 1-5	4.2 ± 0.9	4.2 ± 1.0	4.0 ± 0.9	3.8 ± 0.8** (↓10)
Weeks 1-13	7.4 ± 1.0	7.2 ± 1.2	7.5 ± 1.3	6.7 ± 1.2** (↓9)
Weeks 1-14	7.5 ± 1.1	7.5 ± 1.3	7.4 ± 1.3	6.9 ± 1.2* (↓8)
Weeks 1-21	8.6 ± 1.4	8.3 ± 1.7	8.2 ± 1.4	8.0 ± 1.2* (↓7)
Weeks 1-31	11.8 ± 2.1	11.2 ± 2.4	10.8 ± 2.2* (↓8)	10.0 ± 1.8** (↓15)
Weeks 1-53	14.3 ± 3.4	14.0 ± 3.1	14.1 ± 3.0	12.6 ± 2.5** (↓12)
Weeks 1-65	15.7 ± 3.5	14.9 ± 3.2	15.1 ± 2.8	13.8 ± 2.6** (↓12)
Weeks 1-81	16.3 ± 3.8	16.5 ± 3.7	16.9 ± 3.1	14.7 ± 3.3* (↓10)

a Data (n = 42-50) were obtained from Table 8 on pages 63-72 of MRID 46800233. Percent differences from controls, calculated by the reviewers, are included in parentheses.

* Significantly different from controls at p#0.05

** Significantly different from controls at p#0.01

TABLE 4c. Group mean (not adjusted) body weight gains (g) at selected intervals in mice fed NOA 446510 in the diet for up to 80 weeks[a]

Weeks	Dose (ppm)							
	Males				Females			
	0	100	500	2000	0	100	500	2000
1-13	10.0	10.0	10.0	9.6	7.4	7.2	7.5	6.8
13-25	4.7	4.6	4.9	3.6	2.4	2.6	2.2	2.0
25-39	4.1	4.0	4.6	3.6	3.0	2.8	2.5	2.5
39-51	2.8	2.8	3.5	2.7	1.7	1.5	2.1	1.7
51-65	0.3	-0.5	0.0	-0.1	1.2	0.8	0.9	0.8
65-81	0.6	1.3	-0.3	1.1	0.6	1.5	1.7	1.0
1-81	22.5	22.2	22.7	20.5(↓9)	16.3	16.4	16.9	14.8(↓9)

a Number of animals/group = 42-50

Calculations by Reviewer. Percent differences from controls, calculated by Reviewers, are included in parentheses.

C. FOOD CONSUMPTION, FOOD EFFICIENCY, AND COMPOUND INTAKE

1. **Food consumption:** There were no effects of treatment on food consumption.

2. **Food efficiency:** At 2000 ppm, food utilization was decreased ($p \leq 0.05$) in the males for Weeks 9-13 (↓20%) and Weeks 1-13 (↓5%) and in the females for Weeks 1-4 (↓12%; Table 5). Food utilization was also decreased by 5% ($p \leq 0.05$) in the males at 500 ppm for Weeks 1-13; however, this decrease did not reflect adverse effects on body weights or body weight gains at this dose.

TABLE 5. Mean (±SD) food utilization (g food/100 g body weight gain) in mice fed NOA 446510 in the diet for up to 80 weeks [a]

Study Interval	Dose (ppm)			
	0	100	500	2000
Males				
Weeks 1-4	4.98 ± 0.73	5.12 ± 0.49	5.16 ± 0.41	4.96 ± 0.79
Weeks 5-8	2.51 ± 0.59	2.37 ± 0.65	2.21 ± 0.46	2.39 ± 0.44
Weeks 9-13	1.59 ± 0.44	1.72 ± 0.56	1.37 ± 0.65	1.27 ± 0.43* (↓20)
Weeks 1-13	2.92 ± 0.16	2.95 ± 0.28	2.78 ± 0.30* (↓5)	2.76 ± 0.19* (↓5)
Females				
Weeks 1-4	3.95 ± 0.71	4.13 ± 0.73	3.90 ± 0.66	3.48 ± 0.33* (↓12)
Weeks 5-8	1.64 ± 0.47	1.69 ± 0.40	1.87 ± 0.73	1.69 ± 0.56
Weeks 9-13	1.03 ± 0.33	1.19 ± 0.40	0.96 ± 0.51	0.86 ± 0.31
Weeks 1-13	2.10 ± 0.30	2.23 ± 0.31	2.10 ± 0.16	1.91 ± 0.17

a Data (n = 10) were obtained from Table 10 on pages 81-82 of MRID 46800233. Percent differences from controls, calculated by the reviewers, are included in parentheses.

* Significantly different from controls at p#0.05

2. **Compound consumption:** Compound intake values (mg/kg/day) are presented in Table 1 of this DER.

D. **HEMATOLOGY:** The numbers of leukocytes and lymphocytes were decreased ($p \leq 0.05$) by 26-29% in the 500 and 2000 ppm females (Table 6). The number of lymphocytes was also decreased by 26% at 100 ppm, but did not reflect a decrease in the total number of white blood cells at this dose. The statistical analysis was repeated, excluding individual females with low values (#206, 246, and 286 for leukocytes and #206 for lymphocytes), which resulted in all treated groups being comparable to controls. However, the Sponsor did not provide an experimental justification for excluding these mice. Even if an outlier test was performed, and these individual values were determined to be statistical outliers, it is not appropriate to exclude them from the analyses simply to alleviate any statistical differences. However, it can be concluded that these differences were attributed to only a few animals (1-3 out of 41-45). There were no other statistically ($p \leq 0.05$) or biologically significant differences. It should be noted that the standard deviations for control leukocytes and lymphocytes are about equal to the group means (wide range and/or "outliers").

TABLE 6. Selected mean (±SD) hematology findings in female mice fed NOA 446510 in the diet for up to 80 weeks [a]

Parameter	Dose (ppm)			
	0	100	500	2000
Leukocytes (10^9/L)	2.73 ± 2.61	2.30 ± 1.47	2.02 ± 0.69* (↓26)	1.98 ± 0.62* (↓27)
Lymphocytes (10^9/L)	2.05 ± 1.99	1.52 ± 0.68* (↓26)	1.50 ± 0.52* (↓27)	1.45 ± 0.44* (↑29)

a Data (n = 41-45) were obtained from Table 11 on page 84 of MRID 46800233. Percent differences from controls, calculated by the reviewers, are included in parentheses.

* Significantly different from controls at p#0.05

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E. SACRIFICE AND PATHOLOGY

1. **Organ weight:** Absolute, relative to body weight, and adjusted for initial body weight liver weights were increased in the males at 500 ppm (↑11-12%) and in both sexes at 2000 ppm (↑7-15%; Table 7). These increases were significant ($p \leq 0.05$) except for absolute weights in the 2000 ppm males (relative liver weights were not examined statistically). Regardless of the percent increases and/or statistical significance, there did not appear to be an adverse or biologically significant affect on liver weights. Additionally, a number of organ weights differed significantly ($p \leq 0.05$) from controls but were considered unrelated to treatment because they were not corroborated by treatment-related clinical, macroscopic, or microscopic findings.

TABLE 7. Mean (±SD) liver weights in mice fed NOA 446510 in the diet for up to 80 weeks [a]

Parameter	Dose (ppm)			
	0	100	500	2000
Males				
Terminal body weight (g)	44.5 ± 6.4	43.7 ± 5.0	44.3 ± 6.7	41.9 ± 5.2
Liver				
absolute (g)	1.84 ± 0.32	1.76 ± 0.27	2.04 ± 0.67* (↑11)	1.98 ± 0.38 (↑8)
relative to BW (%)	4.14 ± 0.37	4.03 ± 0.40	4.61 ± 1.14 (↑11)	4.70 ± 0.49 (↑14)
adjusted for BW (g)	1.80	1.75	2.01** (↑12)	2.07** (↑15)
Females				
Terminal body weight (g)	33.8 ± 4.1	34.4 ± 4.1	34.9 ± 3.7	32.8 ± 3.5
Liver				
absolute (g)	1.23 ± 0.14	1.25 ± 0.28	1.28 ± 0.16	1.32 ± 0.13* (↑7)
relative to BW (%)	3.67 ± 0.45	3.66 ± 0.80	3.69 ± 0.39	4.06 ± 0.36 (↑11)
adjusted for BW (g)	1.24	1.25	1.26	1.35** (↑9)

a Data (n = 41-47) were obtained from Table 12 on page 93 of MRID 46800233. Percent differences from controls, calculated by the reviewers, are included in parentheses.

* Significantly different from controls at p#0.05

** Significantly different from controls at p#0.01

2. **Gross pathology:** No macroscopic findings could be attributed to treatment.

2. **Microscopic pathology**

a. Non-neoplastic - There were no treatment-related microscopic findings

b. Neoplastic – Data for intergroup comparison of tumor bearing animals and incidences of neoplastic microscopic findings, found in Tables 16 through 18 on pages 174-179 of the study report, are included as an attachment to this DER. There were no treatment-related tumors.

III. DISCUSSION AND CONCLUSIONS

A. **INVESTIGATOR=S CONCLUSIONS:** It was concluded that the LOAEL was 2000 ppm based on decreased body weights, body weight gains, and food utilization and increased liver weights in both sexes. The liver was considered to be the target organ, and the increases in

liver weight in the 500 ppm males and in both sexes at 2000 ppm were consistent with observations made in previous studies and were considered treatment-related. Based on this evidence of systemic toxicity, the study was considered adequate to assess carcinogenicity. There were no treatment-related increases in the incidence of tumors, no dose-related trend in the number of tumors, and no indication of an altered time to onset of any tumor type.

B. REVIEWER'S COMMENTS: No adverse treatment-related effects were observed on mortality, food consumption, hematology (i.e., leukocyte differential), gross pathology, or histopathology.

An increased frequency of circling behavior was observed in the females at 500 and 2000 ppm. However, this behavior was only slightly increased in incidence at 2000 ppm compared to controls. Dose-related increases in the number of mice with their left ear being torn were observed in both sexes at 500 and 2000 ppm. The number of mice with the right ear torn was minimal in incidence (≤1 mouse/dose group) and did not show a pattern with dose. It was stated that the animals were identified by ear tags, and it is likely that these identification tags were placed in the left ear. The mice were housed together in groups and could have removed the tags (and selectively torn the left ear) of their cage-mates via fighting or other interactions. However, this would not explain why the incidence of this finding was dose-related. The possibility that the test substance increased fighting or some other behavior that led to the left ear being torn cannot be ruled out. However, because there were no dose-related incidences in scabs or other signs of fighting and because there were no clinical signs of neurotoxicity in this study or in the acute or subchronic neurotoxicity studies in rats (MRID 46800240 through 46800242), the toxicological importance of this finding is considered equivocal.

At 2000 ppm, body weights were slightly decreased ($p \leq 0.05$) in the males generally from Weeks 19-35 and in the females during Weeks 4, 5, and 13-81. Body weight gains were decreased at this dose in the males during Weeks 19-79 and in the females during Weeks 4-6 and 11-81. The decreased body weight gains attained statistical significance ($p \leq 0.05$) throughout the study, except at Week 81 in the males and at Week 79 in the females. Food utilization was decreased ($p \leq 0.05$) in the males for Weeks 9-13 (↓20%) and Weeks 1-13 (↓5%) and in the males for Weeks 1-4 (↓12%) and reflected the decrease in body weights at this dose. These decreases in body weights were not considered to be of biological or toxicological significance. Based on 13-week intervals, there was a decrease in body weight gains throughout most of the study.

At 500 ppm, only incidental differences ($p \leq 0.05$) from controls were noted in body weights, body weight gains, and food utilization.

Absolute, relative to body weight, and adjusted for initial body weight liver weights were increased in the males at 500 ppm and in both sexes at 2000 ppm. These increases were significant ($p \leq 0.05$) except for absolute weights in the 2000 ppm males (relative liver weights were not examined statistically). Because of the relatively small increases in liver weights and in the absence of any microscopic findings in the liver, the increased liver weights were not considered adverse but were likely an adaptive response to the presence of the test

substance.

There were no effects of treatment on the incidence or time to onset of any tumor types. Therefore, there was no evidence of a carcinogenic effect.

The LOAEL is 2000 ppm (equivalent to 223/285 mg/kg/day in males/females), based on decreased body weight gain in both sexes and decreased food utilization in males. The NOAEL is 500 ppm (equivalent to 55/68 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

C. **STUDY DEFICIENCIES:** No deficiencies were noted.

ATTACHMENT

The following Tables 16 through 18, pages 174 through 179 are included from the study report.

TABLE 16 INTERGROUP COMPARISON OF TUMOUR BEARING ANIMALS

	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 1	GROUP 2	GROUP 3	GROUP 4
	MALES				FEMALES			
	0 ppm	100 ppm	500 ppm	2000 ppm	0 ppm	100 ppm	500 ppm	2000 ppm
ANIMALS ON STUDY	50	50	50	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50	50	50	50
NUMBER OF TUMOUR BEARING ANIMALS	26	15	25	15	19	17	11	10
ANIMALS WITH MALIGNANT TUMOURS	20	15	21	11	19	17	7	10
BENIGN TUMOURS	8	2	6	4	0	1	4	0
MULTIPLE TUMOURS	3	2	3	1	0	2	0	1
SINGLE TUMOURS	23	13	22	14	19	15	11	9
MULTIPLE MALIGNANT TUMOURS	1	0	1	1	0	1	0	1
MULTIPLE BENIGN TUMOURS	0	0	0	0	0	0	0	0
METASTATIC TUMOURS	19	14	20	11	17	16	7	10

TABLE 17 INTERGROUP COMPARISON OF MICROSCOPIC NEOPLASTIC FINDINGS (SPLIT BY REMOVAL REASON)

REMOVAL REASON: INTERCURRENT	MALES				FEMALES			
	0 ppm	100 ppm	500 ppm	2000 ppm	0 ppm	100 ppm	500 ppm	2000 ppm
ANIMALS ON STUDY	50	50	50	50	50	50	50	50
ANIMALS COMPLETED	5	3	8	6	6	5	5	7
HARDERIAN GLAND								
EXAMINED	5	3	8	6	6	5	5	6
MISSING	0	0	0	0	0	0	0	1
Adenoma (BENIGN)	1	0	0	0	0	0	0	0
Adenocarcinoma (MALIGNANT)	0	0	1	0	0	0	0	0
LYMPHORETICULAR SYSTEM								
EXAMINED	2	3	6	2	5	4	0	2
Lymphosarcoma (MALIGNANT)	1	2	3	1	3	1	0	0
Histiocytic sarcoma (MALIGNANT)	1	1	2	1	2	3	0	2
OVARY								
EXAMINED	-	-	-	-	6	4	5	5
MISSING	-	-	-	-	0	1	0	2
Malignant granulosa/theca cell tumour (MALIGNANT)	-	-	-	-	0	1	0	0
SPLEEN								
EXAMINED	5	3	8	6	6	4	5	6
MISSING	0	0	0	0	0	1	0	1
Haemangiosarcoma (MALIGNANT)	0	0	0	0	1	0	0	0

TABLE 17 INTERGROUP COMPARISON OF MICROSCOPIC NEOPLASTIC FINDINGS (SPLIT BY REMOVAL REASON)

REMOVAL REASON: TERMINAL	MALES				FEMALES			
	0 ppm	100 ppm	500 ppm	2000 ppm	0 ppm	100 ppm	500 ppm	2000 ppm
ANIMALS ON STUDY	50	50	50	50	50	50	50	50
ANIMALS COMPLETED	45	47	42	44	44	45	45	43
HARDERIAN GLAND								
EXAMINED	44	47	41	44	43	45	45	42
MISSING	1	0	1	0	1	0	0	1
Adenoma..(BENIGN)	2	0	2	2	0	0	0	0
HEART								
EXAMINED	45	47	42	44	44	45	45	43
Haemangioma..(BENIGN)	1	0	0	0	0	0	0	0
LIVER								
EXAMINED	45	47	42	44	44	45	45	43
Hepatocellular adenoma..(BENIGN)	0	0	1	1	0	0	0	0
Haemangiosarcoma..(MALIGNANT)	1	0	0	1	0	1	0	1
LUNG								
EXAMINED	45	47	42	44	44	45	45	43
Adenoma..(BENIGN)	3	2	3	3	0	0	1	0
Adenocarcinoma..(MALIGNANT)	1	1	0	0	1	0	0	0
LYMPHORETICULAR SYSTEM								
EXAMINED	17	11	15	9	12	11	7	8
Lymphosarcoma..(MALIGNANT)	15	9	7	8	8	7	4	5
Histiocytic sarcoma..(MALIGNANT)	2	2	8	3	4	5	3	3
OVARY								
EXAMINED	-	-	-	-	43	44	42	43
MISSING	-	-	-	-	1	1	3	0
Tubulostromal adenoma (BENIGN)	-	-	-	-	0	0	1	0
PITUITARY GLAND								
EXAMINED	42	40	38	38	41	40	44	39
MISSING	3	7	4	6	3	5	1	4

TABLE 17 INTERGROUP COMPARISON OF MICROSCOPIC NEOPLASTIC FINDINGS (SPLIT BY REMOVAL REASON)

REMOVAL REASON: TERMINAL	MALES				FEMALES			
	0 ppm	100 ppm	500 ppm	2000 ppm	0 ppm	100 ppm	500 ppm	2000 ppm
ANIMALS ON STUDY	50	50	50	50	50	50	50	50
ANIMALS COMPLETED	45	47	42	44	44	45	45	43
PITUITARY GLAND	(CONTINUED)							
Adenoma..(BENIGN)	1	0	0	0	0	1	0	0
SKIN								
EXAMINED	45	47	42	44	44	45	45	43
Haemangioma..(BENIGN)	0	0	0	0	0	0	1	0
SPLEEN								
EXAMINED	45	47	42	44	44	44	45	43
MISSING	0	0	0	0	0	1	0	0
Haemangiosarcoma..(MALIGNANT)	0	0	1	0	0	0	0	0
THYROID GLAND								
EXAMINED	45	46	39	43	44	44	45	43
MISSING	0	1	3	1	0	1	0	0
Follicular cell adenoma..(BENIGN)	0	0	0	0	0	0	1	0

TABLE 18 INTERGROUP COMPARISON OF MICROSCOPIC NEOPLASTIC FINDINGS (TOTAL)

	MALES				FEMALES			
	0 ppm	100 ppm	500 ppm	2000 ppm	0 ppm	100 ppm	500 ppm	2000 ppm
ANIMALS ON STUDY	50	50	50	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50	50	50	50
HARDERIAN GLAND								
EXAMINED	49	50	49	50	49	50	50	48
MISSING	1	0	1	0	1	0	0	2
Adenoma..(BENIGN)	3	0	2	2	0	0	0	0
Adenocarcinoma..(MALIGNANT)	0	0	1	0	0	0	0	0
HEART								
EXAMINED	50	50	50	50	50	50	50	50
Haemangioma..(BENIGN)	1	0	0	0	0	0	0	0
LIVER								
EXAMINED	50	50	50	50	50	50	50	49
MISSING	0	0	0	0	0	0	0	1
Hepatocellular adenoma..(BENIGN)	0	0	1	1	0	0	0	0
Haemangiosarcoma..(MALIGNANT)	1	0	0	1	0	1	0	1
LUNG								
EXAMINED	50	50	50	50	50	50	50	49
MISSING	0	0	0	0	0	0	0	1
Adenoma..(BENIGN)	3	2	3	1	0	0	1	0
Adenocarcinoma..(MALIGNANT)	1	1	0	0	1	0	0	0
LYMPHORETICULAR SYSTEM								
EXAMINED	13	14	20	11	17	15	7	10
Lymphosarcoma..(MALIGNANT)	10	11	10	9	11	8	4	5
Histiocytic sarcoma..(MALIGNANT)	3	3	10	2	6	8	3	5
OVARY								
EXAMINED	-	-	-	-	49	48	47	49
MISSING	-	-	-	-	1	2	3	2
Malignant granulosa/theca cell tumour (MALIGNANT)	-	-	-	-	0	1	0	0

TABLE 18 INTERGROUP COMPARISON OF MICROSCOPIC NEOPLASTIC FINDINGS (TOTAL)

	MALES				FEMALES			
	0 ppm	100 ppm	500 ppm	2000 ppm	0 ppm	100 ppm	500 ppm	2000 ppm
ANIMALS ON STUDY	50	50	50	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50	50	50	50
OVARY (CONTINUED)								
Tubulostromal adenoma..(BENIGN)	-	-			0	0	1	0
PITUITARY GLAND								
EXAMINED	47	42	44	43	47	44	49	43
MISSING	3	8	6	7	3	6	1	7
Adenoma..(BENIGN)	1	0	0	0	0	1	0	0
SKIN								
EXAMINED	50	50	50	50	50	50	50	50
Haemangioma..(BENIGN)	0	0	0	0	0	0	1	0
SPLEEN								
EXAMINED	50	50	50	50	50	48	50	49
MISSING	0	0	0	0	0	2	0	1
Haemangiosarcoma..(MALIGNANT)	0	0	1	0	1	0	0	0
THYROID GLAND								
EXAMINED	50	49	46	48	50	49	50	48
MISSING	0	1	4	2	0	1	0	2
Follicular cell adenoma..(BENIGN)	0	0	0	0	0	0	1	0